



Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 07-134-849

TÍTULO SOLICITADO: DERIVADOS NOVEDOSOS DE 2-AZETIDINONA
COMO INHIBIDORES DE LA ABSORCIÓN DE
COLESTEROL PARA EL TRATAMIENTO DE
AFECCIONES HIPERLIPIDÉMICAS"

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PRIORIDAD: SE 0501468-3 de 22/06/2005

SOLICITANTE: ASTRAZENECA AB

APODERADO: JUAN PABLO CADENA SARMIENTO

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

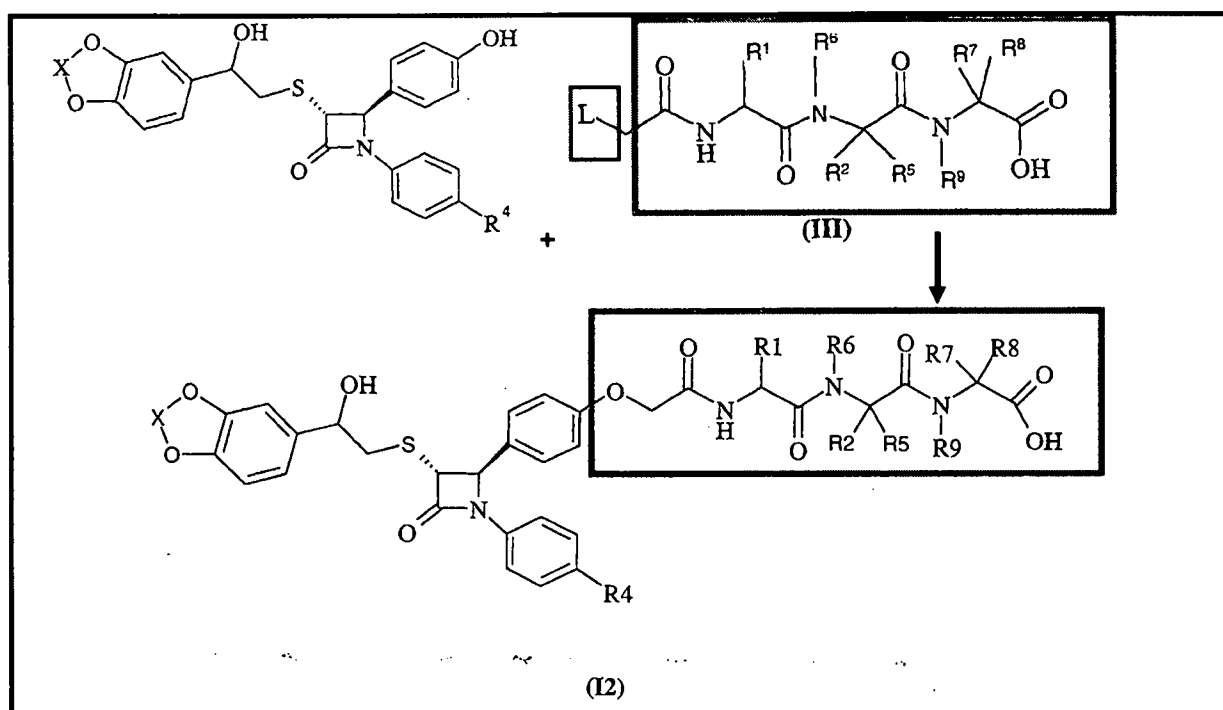
I. COMPLEMENTO DE INFORMACIÓN

Comendidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

Los compuestos que reivindica la solicitud colombiana **07-134-849** que resultan ser análogos de ezetimibe (con un átomo de azufre en vez de un carbono en la posición 3 respecto al núcleo de azetidinona) útiles como inhibidores de la absorción de colesterol en el tratamiento de hiperlipidemia, arteriosclerosis, alzheimer, tumores asociados con colesterol, sus formulaciones farmacéuticas, sus combinaciones con agonistas PPAR alfa y/o gamma o inhibidores de HMG Co-A reductasa y su proceso de obtención, carecen de novedad y nivel inventivo como se argumenta a continuación:

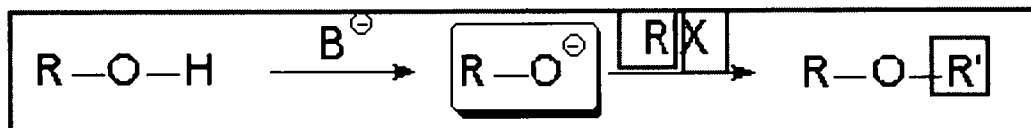
1. En primer término, todos los compuestos así como los procesos de obtención que se reivindican en la solicitud en trámite resultan ser simples intermediarios en la obtención de análogos de ezetimibe, procesos que constan de reacciones de síntesis muy comunes, veamos:

Rv 18 Proceso 1:

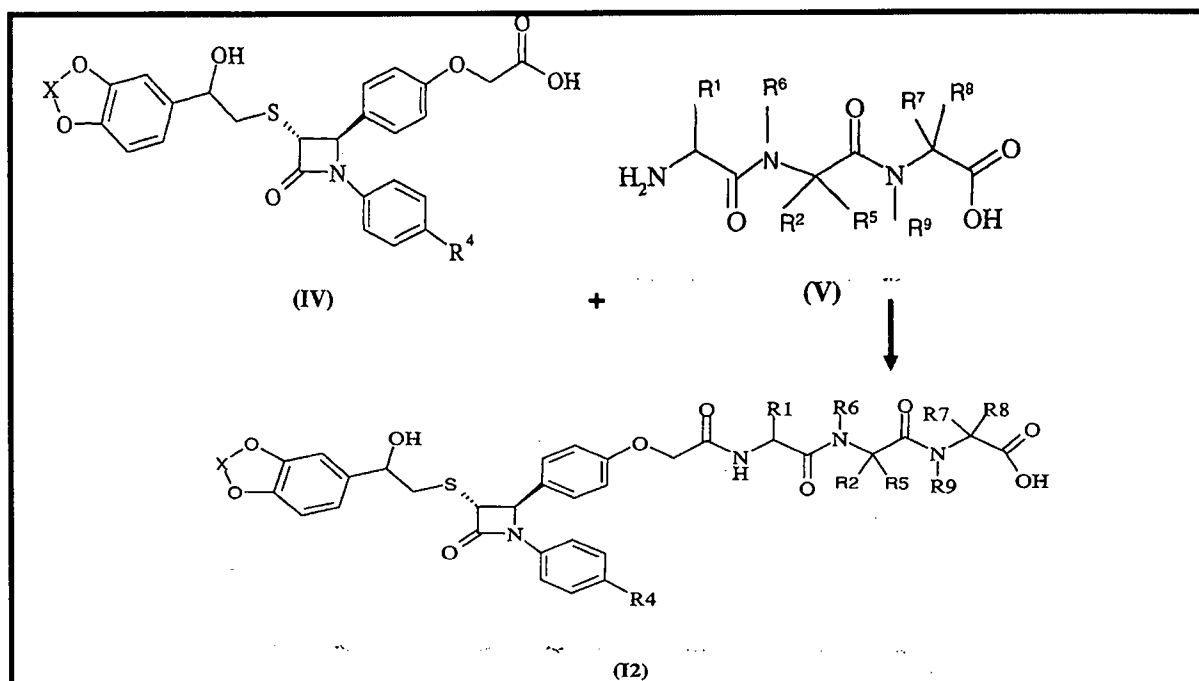


En la solicitud colombiana en trámite, el hidroxilo del grupo hidroxifenil que sustituye al núcleo de azetidinona en posición 4 reacciona con el compuesto de fórmula (III) (donde L es un grupo desplazable o saliente) donde al parecer por sustitución nucleofílica (S_N2) se puede obtener el compuesto de fórmula (I2) (éter alquil sustituido arílico). Este procedimiento corresponde en síntesis orgánica a la

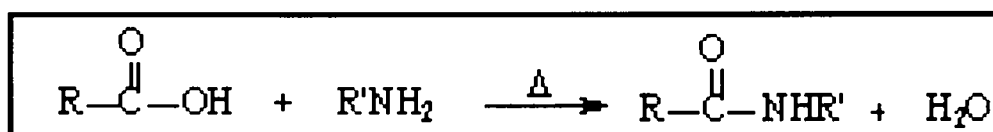
manera más sencilla de preparar un éter, haciendo reaccionar un alcóxido con un haluro o sulfonato de alquilo en una secuencia típica SN2.



Rv 18 Proceso 2:

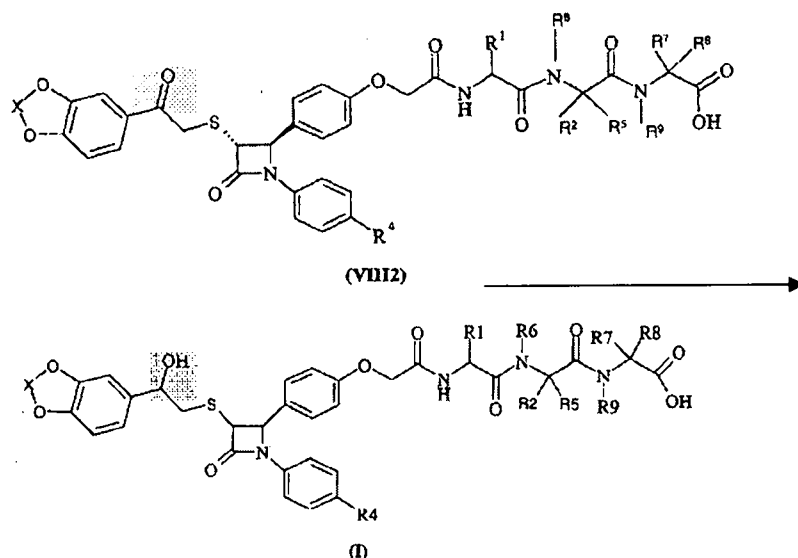


Como se puede apreciar, en la solicitud colombiana en trámite se hace reaccionar el ácido carboxílico de fórmula (IV) o su respectivo derivado éster con una amina de fórmula (V) para obtener el compuesto de fórmula (I) (amida). En síntesis orgánica esto corresponde a la forma más común de preparar una amida, haciendo reaccionar un ácido carboxílico o su respectivo éster con una amina.

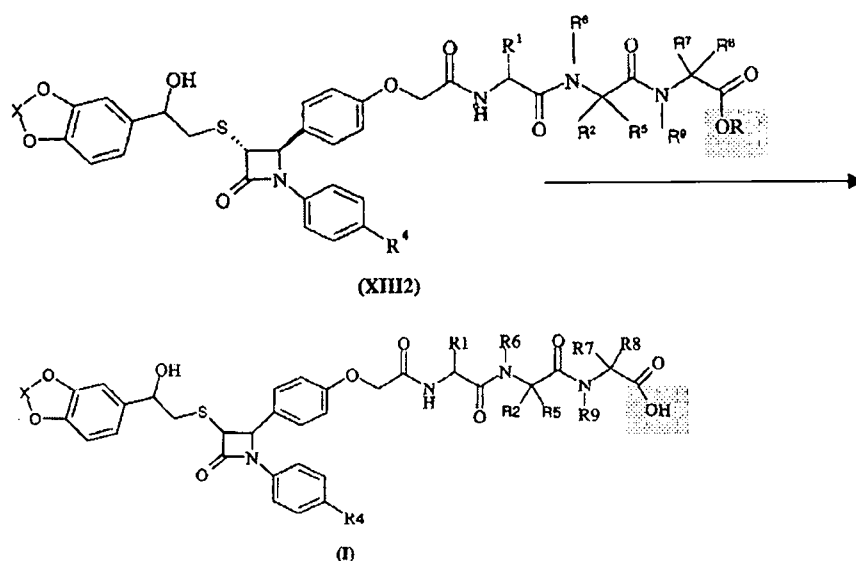


Adicional a lo anterior, se puede observar que dicho tipo de reacciones simples para la preparación de amidas se aplican de la misma forma en los procesos 3 y 3ª, en donde los compuestos de fórmula VI2 y VI2a corresponden a los ácidos carboxílicos y los compuestos VII y VIIa corresponden a las aminas, respectivamente.

De la misma manera, no se puede atribuir nivel inventivo a los procesos 4 y 7 los cuales, respectivamente, se refieren a un proceso de reducción convencional de un grupo carbonilo:

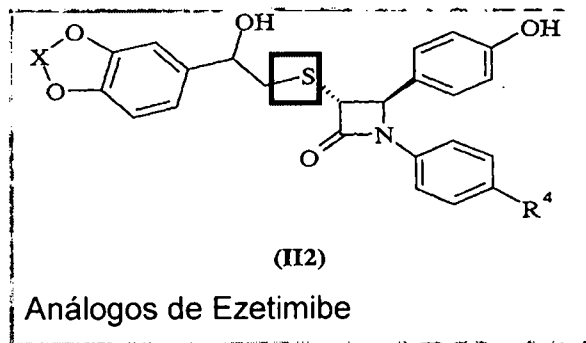
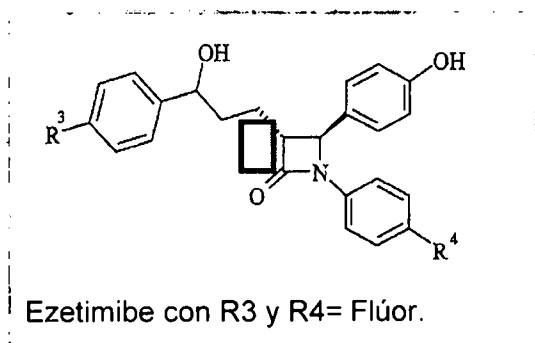


Y de una simple desesterificación:



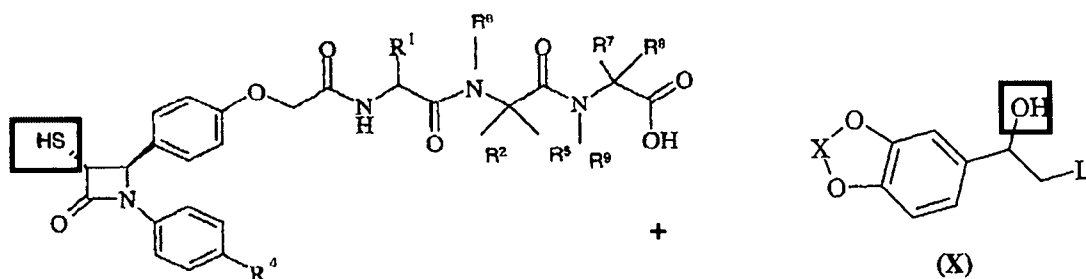
En otro aspecto, es importante resaltar que la analogía de estos compuestos con ezetimibe (resaltada en rojo), consiste, como toda persona versada en la materia reconoce, en el cambio bioisostérico de átomos o grupos de átomos en un fármaco, que presentan propiedades fisicoquímicas y biológicas similares¹,

¹ http://www.qo.fcen.uba.ar/Cursos/quimed_files/QM5.pdf

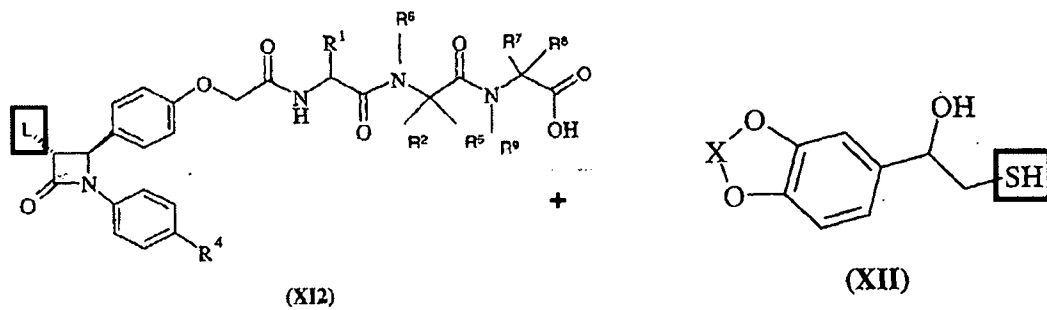


a través de una reacción típica de sustitución nucleofílica de un grupo desplazable L, por el átomo de azufre de un grupo SH, tal como se pretende hacer en el proceso 5 y 6 de la solicitud colombiana en trámite:

Proceso 5:



Proceso 6:



Del mismo modo se debe tener en cuenta que los isómeros más reconocidos son:

Isósteros clásicos

1. Átomos y grupos univalentes
 - a. CH_3 NH_2 OH F Cl
 - b. Cl PH_2 SH
 - c. Br $i\text{-Pr}$
 - d. I $t\text{-Bu}$
2. Átomos y grupos bivalentes
 - a. $\text{—CH}_2\text{—}$ —NH— —O— —S— —Se—
 - b. $\text{—COCH}_2\text{R}$ —CONHR $\text{—CO}_2\text{R}$ —COSR
3. Átomos y grupos trivalentes
 - a. —CH= —N=
 - b. —P= —As=
4. Átomos tetravalentes
 - a. —C— —Si—
 - b. =C= =N= =P=
5. Equivalentes de anillos
 - a. —CH=CH— —S— (ej. benceno, tiofeno)
 - b. —CH= —N= (ej. benceno, piridina)
 - c. —O— —S— $\text{—CH}_2\text{—}$ —NH— (ej. tetrahydrofurano, tetrahydrotiofeno, ciclopentano, pirrolidina)

Es así que los compuestos obtenidos en estos procesos podrían describirse como profármacos de compuestos bioisómeros o análogos a ezetimibe, que son hidrolizables fisiológicamente en el enlace formado por el grupo hidroxilo del sustituyente hidroxifenil de la posición 4 del núcleo de azetidinona de dichos compuestos.

Los profármacos, como toda persona versada en la materia sabe, son derivados terapéuticamente inactivos de un principio activo que mediante bioconversión, o sea, transformación química o enzimática en un medio biológico regeneran la sustancia activa. Entonces, siendo el uso de los cambios isostéricos (*Langmuir 1919* y *Erlenmeyer 1932*¹) y la formación de profármacos (reconocidos y definidos por *Albert*² desde 1958) herramientas ampliamente reconocidas para dar solución a diversas eventualidades de una molécula con actividad farmacológica, no puede entonces atribuírsele nivel inventivo a un proceso de obtención de compuestos análogos de ezetimibe que se obtienen a través de dichos cambios bioisostéricos, o a sus profármacos a través de reacciones sencillas de sustitución y esterificación o formación simple de amidas.

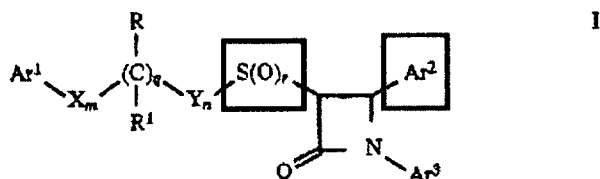
2. La patente americana US 5,633,246 publicada el 27 de mayo de 1997 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUND USEFUL AS HYPOCHOLERESTOLEMIC AGENTS" se refiere a compuestos de la fórmula:

² ALBERT A. Chemical aspects of selective toxicity. Nature 182, 421 (1958).

[57]

ABSTRACT

Sulfur-substituted azetidinone hypocholesterolemic agents
of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

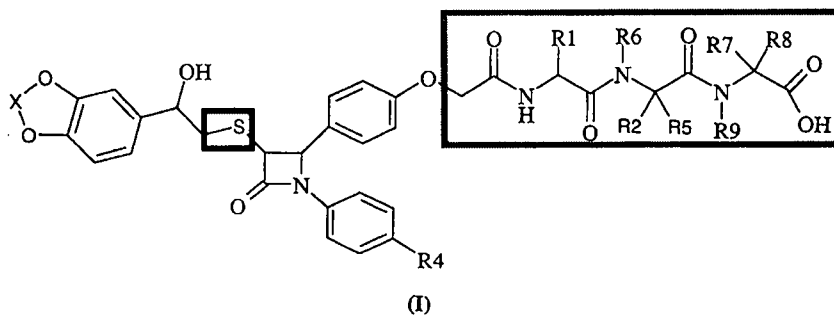
Ar³ is aryl or R⁵-substituted aryl;

q is 0 or 1; r is 0, 1 or 2; m and n are 0-5; provided that the sum of m, n and q is 1-5;

R⁴ is selected from lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁-₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₀-₂R⁹, —O(CH₂)₁-₁₀—COOR⁶, —O(CH₂)₁-₁₀CONR⁶R⁷, (lower alkylene), —COOR⁶ and —CH=CH—COOR⁶;

R⁵ is selected from —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁-₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₀-₂R⁹, —O(CH₂)₁-₁₀—COOR⁶, —O(CH₂)₁-₁₀CONR⁶R⁷, —CF₃, —CN, —NO₂,

(Patente americana US 5,633,246)

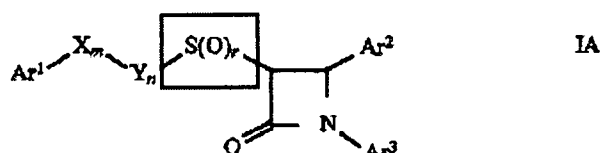


(Solicitud colombiana en trámite)

Como observamos, tanto la patente americana como la solicitud colombiana en trámite permiten la obtención de derivados de azetidinona sustituidos con un átomo de azufre en la posición 3 (rojo), así como de compuestos con

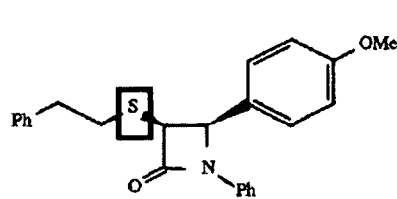
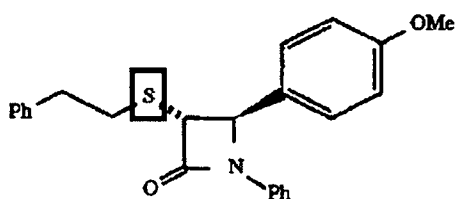
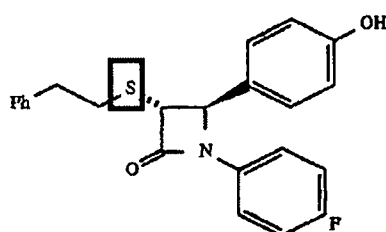
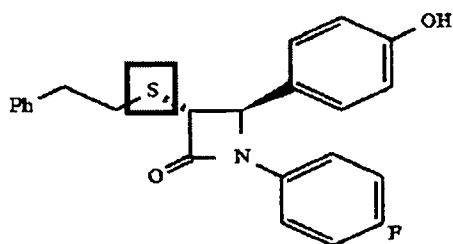
sustituyentes con características químicas similares en la misma posición 4 correspondiente al grupo hidroxifenil (verde).

De la misma manera, en el capítulo descriptivo de la anterioridad mencionada se hacen más evidentes las similitudes entre las características de los compuestos de la patente americana y de la solicitud colombiana, en especial en lo que respecta a que los compuestos poseen el mismo núcleo de azetidina principal, el cual a su vez cuenta con la presencia del átomo de azufre:



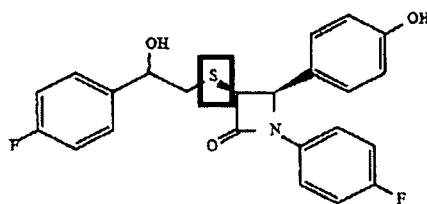
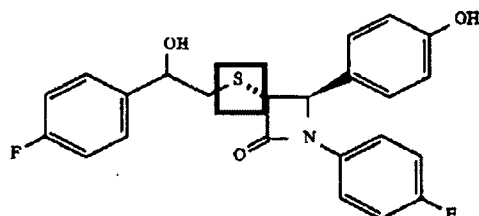
In compounds of formula IA, the sum of m and n is preferably 2, 3 or 4, more preferably 2. Also preferred are compounds wherein the sum of m and n is 2, and r is 0 or 1.

EXAMPLE 1



EXAMPLE 6

EXAMPLE 19



Así mismo, haciendo un paralelo entre lo reivindicado en la solicitud colombiana en trámite y la patente americana podemos evidenciar muchas cosas en común entre los compuestos análogos de ambas partes, veamos:

SOLICITUD COLOMBIANA EN TRAMITE	PATENTE AMERICANA US 5,633,246
15. Una formulación farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 10 en mezcla con coadyuvantes, diluyentes y/o vehículos farmacéuticamente aceptables.	In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.
12. Un método de tratar o prevenir arteriosclerosis que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 10 a un mamífero necesitado de ello.	The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a sulfur-substituted azetidinone cholesterol
17. Una combinación de un compuesto de acuerdo con la formula (I) o (I2) con un inhibidor de HMG Co-A reductasa.	Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981; HMG CoA synthetase inhibitors.

Si bien es cierto que los compuestos descritos en esta anterioridad no corresponden estrictamente a los mismos de la solicitud colombiana en trámite, la información que en esta anterioridad se expone demuestra que existen compuestos análogos relacionados estructuralmente (que además tienen la misma actividad farmacológica y sirven para los mismos tratamientos terapéuticos), y que los procesos que allí se describen para su obtención, son una clara guía para la obtención de los compuestos correspondientes a la solicitud colombiana, lo que en consecuencia afecta el nivel inventivo de dicha invención.

3. Otra publicación donde se pueden observar compuestos análogos a los reivindicados por la solicitud colombiana e información respecto a su obtención es la publicación internacional WO 2004/005247 publicada el 15 de enero de 2004 y titulada “DIPHENYL AZETIDINONE DERIVATIVES FOR TREATING DISORDERS OF THE LIPID METABOLISM”.

4. En el mismo sentido, y siendo la obtención de estos compuestos -azetidinona sustituidos con un átomo de azufre en la posición 3- al parecer el fundamento central de novedad y nivel inventivo de esta solicitud colombiana en trámite, a continuación se demuestra con una publicación científica que estos compuestos derivados de azetidinona con un átomo de azufre son ampliamente reconocidos y caracterizados, y que por lo tanto no se puede adjudicar al menos nivel inventivo en su obtención, tal y como pretende la solicitud colombiana en cuestión:

SYNTHESIS OF C3 HETEROATOM-SUBSTITUTED AZETIDINONES THAT DISPLAY POTENT CHOLESTEROL ABSORPTION INHIBITORY ACTIVITY³.

Abstract: The C3 phenylpropyl side chain of N-phenylazetidinones related to SCH 56524 was modified by replacing the hydroxymethylene with various isoelectronic or isosteric groups. Modifications at the 3' position led to less-active compounds; however, modifications at the 1' position provided compounds with improved cholesterol absorption inhibitory activity. An enantioselective route for the synthesis of C3 1'-sulfur-substituted azetidinones and the development of structure-activity relationships for this series of compounds are presented.

5. Por último, la solicitud colombiana en trámite en sus reivindicaciones 11 a 14 reivindican un método para tratar o prevenir enfermedades como las relacionadas a la hiperlipidemia, arteriosclerosis, Alzheimer y tumores asociados a colesterol; lo cual va en contra de lo dispuesto por el literal d) del artículo 20 de la decisión 486 de la comunidad andina de naciones en donde claramente se expone que “*No serán patentables: los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales.*”

En conclusión, la solicitud colombiana en trámite carece completamente de nivel inventivo, puesto que en el estado de la técnica se encuentran procesos de obtención de compuestos análogos con las mismas características terapéuticas, y obtenidos a través de las mismas estrategias (cambios bioisostéricos) y reacciones que las utilizadas por los procesos reivindicados en dicha solicitud colombiana.

Por todo lo anterior reitero que la solicitud de la referencia, en todas sus reivindicaciones, incumple los requisitos materiales de patentabilidad establecidos

³ **Synthesis of C3 heteroatom-substituted azetidinones that display potent cholesterol absorption inhibitory activity.** (eng; includes abstract) By McKittrick BA, Journal Of Medicinal Chemistry [J Med Chem], 1998 Feb 26; Vol. 41 (5), pp. 752-9; PMID: 9513603

por la Decisión 486 de 2000, razón por la cual no puede ser objeto de privilegio de patente de invención.

VI. ANEXOS

- La patente americana US 5,633,246 del 27 de Mayo de 1997 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUND USEFUL AS HYPOCHOLERESTOLEMIC AGENTS" paginas 3, 4, 6, 7, 9 y 13.
- La publicación científica SYNTHESIS OF C3 HETEROATOM-SUBSTITUTED AZETIDINONES THAT DISPLAY POTENT CHOLESTEROL ABSORPTION INHIBITORY ACTIVITY, abstract.
- La publicación internacional WO 2004/005247 publicada el 15 de enero de 2004 y titulada "DIPHENYL AZETIDINONE DERIVATIVES FOR TREATING DISORDERS OF THE LIPID METABOLISM" capítulo reivindicatorio.

Señor Superintendente,



JOSÉ LUÍS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A 44.655 del C.S.J.



US005633246A

United States Patent [19]

McKittrick et al.

[11] Patent Number: 5,633,246
[45] Date of Patent: May 27, 1997

[54] **SULFUR-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS**

[75] Inventors: **Brian A. McKittrick**, Bloomfield;
Sundeep Dugar, Bridgewater; **Duane A. Burnett**, Fanwood, all of N.J.

[73] Assignee: **Schering Corporation**, Kenilworth, N.J.

[21] Appl. No.: 463,619

[22] Filed: Jun. 5, 1995

Related U.S. Application Data

- [63] Continuation-in-part of Ser. No. 342,197, Nov. 18, 1994.
[51] Int. Cl.⁶ C07D 205/08; C07D 401/12;
C07D 409/12; A61K 31/395
[52] U.S. Cl. 514/210; 540/360
[58] Field of Search 540/360; 514/210

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WO95/26334	10/1995	WIPO

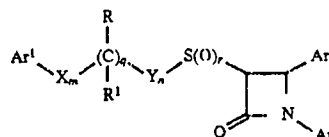
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Primary Examiner—Mark L. Berch
Attorney, Agent, or Firm—Anita W. Magatti; Eric S. Dicker

[57] ABSTRACT

Sulfur-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X and Y are —CH₂—, —CH(lower alkyl)— or —C(dilower alkyl)—;

R is —OR⁶, —O(CO)R⁶, —O(CO)OR⁹ or —O(CO)NR⁶R⁷; R¹ is hydrogen, lower alkyl or aryl; or R and R¹ together are =O;

q is 0 or 1; r is 0, 1 or 2; m and n are 0-5; provided that the sum of m, n and q is 1-5;

R⁴ is selected from lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)—COOR⁶ and —CH=CH—COOR⁶;

R⁵ is selected from —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —CF₃, —CN, —NO₂, halogen, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

R⁶, R⁷ and R⁸ are H, lower alkyl, aryl or aryl-substituted lower alkyl;

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and

R¹⁰ is selected from lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —CF₃, —CN, —NO₂ and halogen;

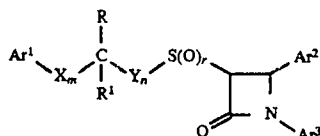
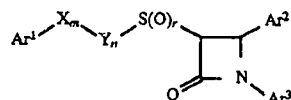
are disclosed, as well as pharmaceutical compositions containing them, and a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor.

5,633,246

3

—O(CO)OR⁹, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷,
 —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶
 (CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷,
 —COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—
 COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —CF₃, —CN,
 —NO₂ and halogen.

Within the scope of formula I, there are two preferred structures. In formula IA, q is zero and the remaining variables are as defined above, and in formula IB, q is 1 and the remaining variables are as defined above:



R⁴, R⁵ and R¹⁰ are each preferably 1-3 independently selected substituents. Preferred are compounds of formula I wherein Ar¹ is phenyl, R¹⁰-substituted phenyl or thienyl, especially (4-R¹⁰)-substituted phenyl or thienyl. Ar² is preferably R⁴-substituted phenyl, especially (4-R⁴)-substituted phenyl. Ar³ is preferably phenyl or R⁵-substituted phenyl, especially (4-R⁵)-substituted phenyl. When Ar¹ is R¹⁰-substituted phenyl, R¹⁰ is preferably halogeno, especially fluoro. When Ar² is R⁴-substituted phenyl, R⁴ is preferably —OR⁶, especially wherein R⁶ is hydrogen or lower alkyl. When Ar³ is R⁵-substituted phenyl, R⁵ is preferably halogeno, especially fluoro. Especially preferred are compounds of formula I wherein Ar¹ is phenyl, 4-fluorophenyl or thienyl, Ar² is 4-(alkoxy or hydroxy)phenyl, and Ar³ is phenyl or 4-fluorophenyl.

X and Y are each preferably —CH₂—. The sum of m, n and q is preferably 2, 3 or 4, more preferably 2. When q is 1, n is preferably 1 to 5.

Preferences for X, Y, Ar¹, Ar² and Ar³ are the same in each of formulae IA and IB.

In compounds of formula IA, the sum of m and n is preferably 2, 3 or 4, more preferably 2. Also preferred are compounds wherein the sum of m and n is 2, and r is 0 or 1.

In compounds of formula IB, the sum of m and n is preferably 1, 2 or 3, more preferably 1. Especially preferred are compounds wherein m is zero and n is 1. R⁴ is preferably hydrogen and R is preferably —OR⁶ wherein R⁶ is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(CO)R⁶, —O(CO)OR⁹ and —O(CO)NR⁶R⁷, defined above), or R and R¹ together form a =O group.

This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a sulfur-substituted azetidinone cholesterol

4

absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.

In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl.

"Heteroaryl" means pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl. All positional isomers wherein the heteroaryl ring is attached through a carbon atom are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl, and 2-thienyl and 3-thienyl. "Halogeno" means fluorine, chlorine, bromine or iodine atoms.

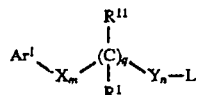
The above statement, wherein R⁶, R⁷ and R⁸ are said to be independently selected from a group of substituents, means that R⁶, R⁷ and R⁸ are independently selected, but also that where an R⁶, R⁷ or R⁸ variable occurs more than once in a molecule, those occurrences are independently selected (e.g., if R is —OR⁶ wherein R⁶ is hydrogen, R⁴ can be —OR⁶ wherein R⁶ is lower alkyl).

Compounds of the invention have at least one asymmetric atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting chiral starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in

7

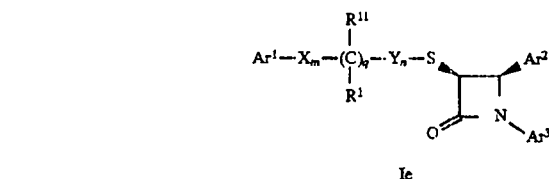
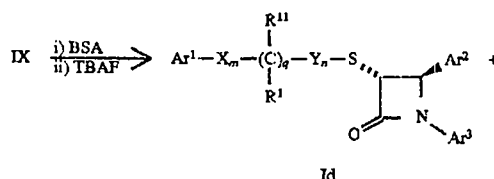
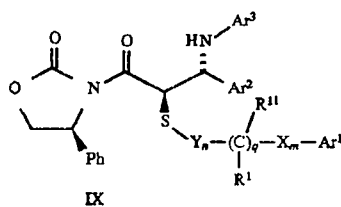
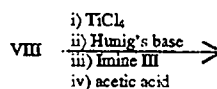
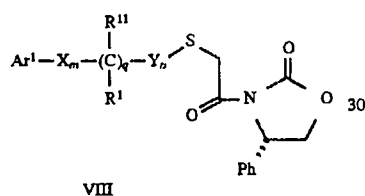
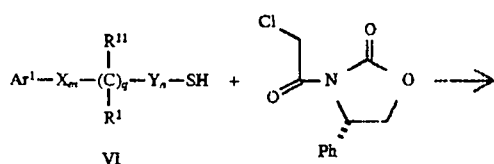


wherein L is a leaving group such as bromo or iodo.

Using the methods described in Method A, compounds of formula Ia prepared by Method B can be converted to sulfinyl and sulfonyl compounds, compounds wherein R and R¹ are =O can be converted to compounds wherein R is H and R¹ is OH, and compounds wherein R is hydroxy can be converted to functionalized hydroxy groups.

Method C:

Compounds of formula I wherein r is zero and the remaining variables are as defined above can be prepared in an enantioselective manner as follows:

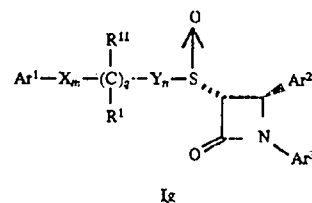
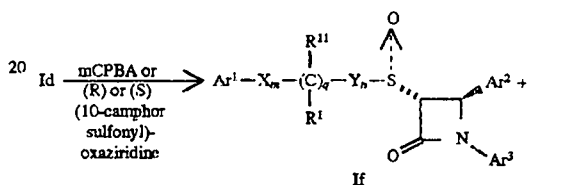


The chloroacetylated oxazolidinone auxiliary of formula VII is reacted with the mercaptan of formula VI, wherein the variables are as defined above, in the presence of a base such as triethylamine in an inert solvent such as CH₂Cl₂. The resultant compound of formula VIII is treated with TiCl₄ in

8

the presence of a base such as diisopropylethylamine (Hunig's base), reacted with an imine of formula III, and then the reaction is quenched with an acid such as acetic acid. The resulting compound of formula IX is then cyclized by reaction with a silylating agent such as bis(trimethylsilyl) acetamide (BSA) and a fluoride catalyst such as tetra butyl ammonium fluoride (TBAF). The cyclization product is separated into cis and trans isomers of formulae Id and Ie using conventional purification techniques, e.g., flash chromatography.

Compounds of formulae Id and Ie can be converted to the corresponding sulfinyl and sulfonyl compounds by reaction with a peracid as described above or with a reagent such as (R) or (S) (10-camphor-sulfonyl)oxaziridine. For example, a compound of formula Id can be converted to the corresponding sulfinyl compounds, If and Ig, as follows:



Before or after separation into cis and trans isomers, as suitable, compounds of formulae Id and Ie can be deprotected at R¹¹, and compounds wherein R is OH can be functionalized as described in Method A.

Starting compounds II, III, IV, VI and VII are all either commercially available, well known in the art, or are prepared via known methods.

Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 1 shows some typical protecting groups:

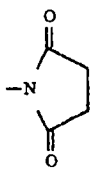
TABLE 1

Group to be Protected	Group to be Protected and Protecting Group
-COOH	-COOalkyl, -COObenzyl, -COOphenyl
NH	NCOalkyl, NCObenzyl, NCOphenyl
	NCH ₂ OCH ₂ CH ₂ Si(CH ₃) ₃ , NC(O)OC(CH ₃) ₃
	N-benzyl, NSi(CH ₃) ₃ , NSi(CH ₃) ₂ CH ₃

5,633,246

9

TABLE I-continued

Group to be Protected	Group to be Protected and Protecting Group
-NH ₂	
-OH	-OCH_3 , $\text{-OCH}_2\text{OCH}_3$, $\text{-OSi(CH}_3)_2\text{C(CH}_3)_3$, $\text{-OSi(CH}_3)_3$, or $\text{-OCH}_2\text{phenyl}$

We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesteryl esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the intestinal absorption and/or esterification of cholesterol; they are, therefore, useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

The in vivo activity of the compounds of formula I can be determined by the following procedure:

In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2 mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by intramuscular (IM) injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Lipid analysis is conducted as per published procedures (Schnitzer-Polokoff, R., et al, *Comp. Biochem. Physiol.*, 99A, 4 (1991), p. 665-670) and data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesterolemic dose of a compound of formula I is about 0.1 to about 30 mg/kg of body weight per day, preferably about 0.1 to about 15 mg/kg. For an average body weight of 70 kg, the dosage level is therefore from about 5 mg to about 1000 mg of drug per day, given in a

10

single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

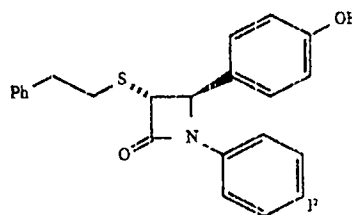
For the combinations of this invention wherein the sulfur-substituted azetidinone is administered in combination with a cholesterol biosynthesis inhibitor, the typical daily dose of the cholesterol biosynthesis inhibitor is 0.1 to 80 mg/kg of mammalian weight per day administered in single or divided dosages, usually once or twice a day; for example, for HMG CoA reductase inhibitors, about 10 to about 40 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 10 to 80 mg per day, and for the other cholesterol biosynthesis inhibitors, about 1 to 1000 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 1 mg to about 2000 mg per day. The exact dose of any component of the combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Where the components of a combination are administered separately, the number of doses of each component given per day may not necessarily be the same, e.g. where one component may have a greater duration of activity, and will therefore need to be administered less frequently.

Since the present invention relates to the reduction of plasma cholesterol levels by treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a cholesterol biosynthesis inhibitor pharmaceutical composition and a sulfur-substituted azetidinone cholesterol absorption inhibitor pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral and parenteral) or are administered at different dosage intervals.

Following are examples of preparing compounds of formula I. The terms *cis* and *trans* refer to the relative orientations at the azetidinone 3- and 4-positions; unless otherwise indicated. The term "J" refers to the proton NMR coupling constant in hertz (Hz) between the 3- and 4-substituted protons of the azetidinone. CD spectra were obtained as solutions in methanol.

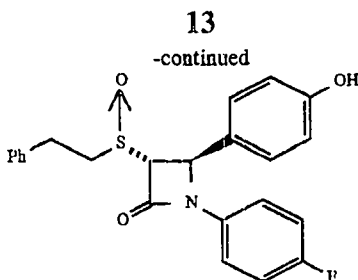
EXAMPLE 1



Step 1: Heat a mixture of 4-fluoroaniline (128 ml) and 4-*t*-butyldimethylsiloxy benzaldehyde (290 g) in toluene (1.2 L) to reflux under a Dean-Stark trap. After 24 h, concentrate in vacuo and dissolve the residue in warm hexane (0.2 L). Cool to -20° C. and collect the resultant imine (378 g, 94% yield) by filtration; mp 51.4°-52.2° C.

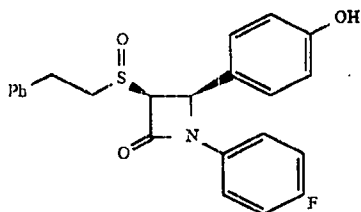
Step 2: To a mixture of phenethylmercapto acetic acid (0.55 g) [prepared in two steps by i) reaction of phenethyl mercaptan and ethyl bromoacetate and ii) saponification with ethanolic aqueous NaOH], the imine prepared in step

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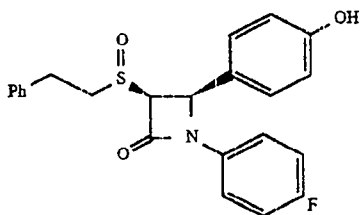


Heat a solution of compound 1 from Example 1 (2.3 g) and (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine (1.48 g) in tetrahydrofuran (THF) (40 ml) to reflux. After 14 h, concentrate the reaction mixture and purify the residue by flash chromatography on silica using CH_2Cl_2 /isopropyl alcohol (100:1) to elute first diastereomer 2a (0.6 g, 25%): Elemental analysis calculated for $\text{C}_{23}\text{H}_{20}\text{NO}_3\text{SF}$: C 67.47, H 4.92, N 3.42; found C 67.12, H 5.02, N 3.43; $[\theta]_D^{25} = +214.4^\circ$ (1.25 mg/ml CH_3OH); $^1\text{H NMR}$ CDCl_3 : 3.15 (m, 3H), 3.92 (m, 2H), 5.25 (d, $J=2.5$ Hz, 1H), 6.0 (bs, 1H), 6.8–6.9 (4H), 7.15–7.35 (8H); CIMS 410(M+H). Next, elute diastereomer 2b, then crystallize diastereomer 2b from isopropyl alcohol (IPA) to give a colorless solid (1.48 g, 62%). Elemental analysis calculated for $\text{C}_{23}\text{H}_{20}\text{NO}_3\text{SF}$: C 67.47, H 4.92, N 3.42; found C 67.28, H 4.89, N 3.45; $[\theta]_D^{25} = +5.56 \times 10^4$, $[\theta]_D^{25} = -2.79 \times 10^4$; $[\alpha]_D^{25} = -16^\circ$ (1.25 mg/ml CH_3OH); $^1\text{H NMR}$ CDCl_3 : 3.1–3.4 (m, 4H), 4.2 (d, $J=2$ Hz, 1H), 5.39 (d, $J=2$ Hz, 1H), 6.7 (d, 2H), 6.95 (m, 2H), 7.15–7.35 (8H); CIMS 410(M+H).

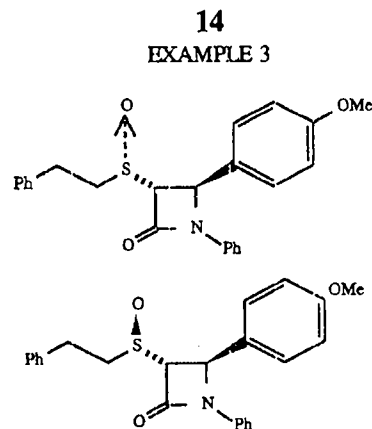
Use the procedure from Example 2 with compound 1a from Example 1 to obtain the following compounds:



2c: Elemental analysis calculated for $\text{C}_{23}\text{H}_{20}\text{NO}_3\text{SF}$: C 67.47, H 4.92, N 3.42, S 7.83; found C 67.21, H 5.0, N 3.5, S 7.48.



2d: Elemental analysis calculated for $\text{C}_{23}\text{H}_{20}\text{NO}_3\text{SF}$: C 67.47, H 4.92, N 3.42, S 7.83; found C 67.5, H 5.11, N 3.6, S 7.71.

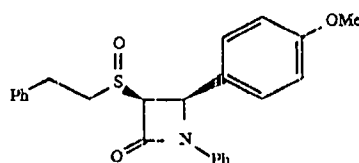


Treat compound 1b from Example 1 (0.36 g) in CH_2Cl_2 (15 ml) at 0°C . with *m*-chloroperbenzoic acid (mCPBA) (0.16 g) at -78°C . After 2 h, add dilute NaHSO_3 and warm the mixture to rt. Partition with EtOAc and sequentially wash the organic layer with 10% NaHCO_3 and brine, then dry (MgSO_4) and concentrate in vacuo. Purify the residue by HPLC on silica using EtOAc/hexane (1:2) to elute compounds 3a (0.185 g) and 3b (0.10 g).

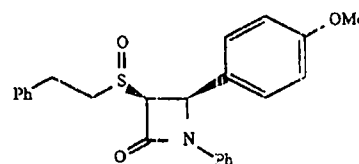
3a: Elemental analysis calculated for $\text{C}_{24}\text{H}_{23}\text{NO}_3\text{S}$: C 71.09, H 5.72, N 3.45; found C 70.87, H 5.55, N 3.52; $[\theta]_D^{25} = -5.36 \times 10^4$, $[\theta]_D^{25} = +5.46 \times 10^4$; $^1\text{H NMR}$ CDCl_3 : 3.15 (m, 3H), 3.8 (s, 3H), 3.9 (m, 1H), 3.94 (d, $J=2.5$ Hz, 1H), 5.33 (d, $J=2.5$ Hz, 1H), 6.9–7.35 (14H).

3b: Elemental analysis calculated for $\text{C}_{24}\text{H}_{23}\text{NO}_3\text{S}$: C 71.09, H 5.72, N 3.45, S 7.83; found C 70.90, H 5.72, N 3.55; $[\theta]_D^{25} = -4.8 \times 10^3$, $[\theta]_D^{25} = +7.4 \times 10^4$, $[\theta]_D^{25} = -4.0 \times 10^4$; $^1\text{H NMR}$ CDCl_3 : 3.18 (m, 4H), 3.8 (s, 3H), 4.12 (d, $J=2$ Hz, 1H), 5.5 (d, $J=2$ Hz, 1H), 6.9–7.35 (14H).

Use the procedure of example 3 with compound 1c obtain the following products:



3c: Elemental analysis calculated for $\text{C}_{24}\text{H}_{23}\text{NO}_3\text{S} \cdot 0.2 \text{H}_2\text{O}$: C 70.46, H 5.77, N 3.42; found C 70.49, H 5.78, N 3.52; $^1\text{H NMR}$ CDCl_3 : 2.85 (m, 1H), 2.95 (m, 1H), 3.12 (m, 1H), 3.62 (m, 1H), 3.8 (s, 3H), 4.4 (d, $J=5.6$ Hz, 1H), 5.35 (d, $J=5.6$ Hz, 1H), 6.9–7.35 (14H).



3d: Elemental analysis calculated for $\text{C}_{24}\text{H}_{23}\text{NO}_3\text{S} \cdot 0.2 \text{H}_2\text{O}$: C 70.46, H 5.77, N 3.42; found C 70.32, H 5.78, N 3.46; $^1\text{H NMR}$ CDCl_3 : 3.17 (m, 3H), 3.4 (m, 1H), 3.83 (s, 3H), 4.69 (d, $J=5.2$ Hz, 1H), 5.55 (d, $J=5.2$ Hz, 1H), 6.95–7.4 (14H); $[\alpha]_D^{25} = -136^\circ$ (CH_3OH).

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1: J Med Chem. 1998 Feb 26;41(5):752-9.



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Synthesis of C3 heteroatom-substituted azetidinones that display potent cholesterol absorption inhibitory activity.

McKittrick BA, Ma K, Huie K, Yumibe N, Davis H Jr, Clader JW, Czarniecki M, McPhail AT.

Schering-Plough Research Institute, Kenilworth, New Jersey 07033, USA.

The C3 phenylpropyl side chain of N-phenylazetidinones related to SCH 56524 was modified by replacing the hydroxymethylene with various isoelectronic or isosteric groups. Modifications at the 3' position led to less-active compounds; however, modifications at the 1' position provided compounds with improved cholesterol absorption inhibitory activity. An enantioselective route for the synthesis of C3 1'-sulfur-substituted azetidinones and the development of structure-activity relationships for this series of compounds are presented.

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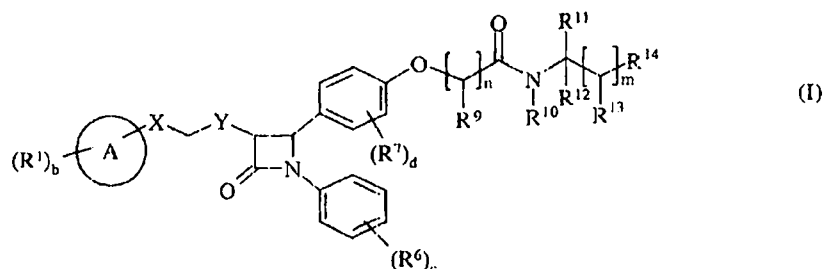
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(54) Title: **DIPHENYLAZETIDINONE DERIVATIVES FOR TREATING DISORDERS OF THE LIPID METABOLISM**

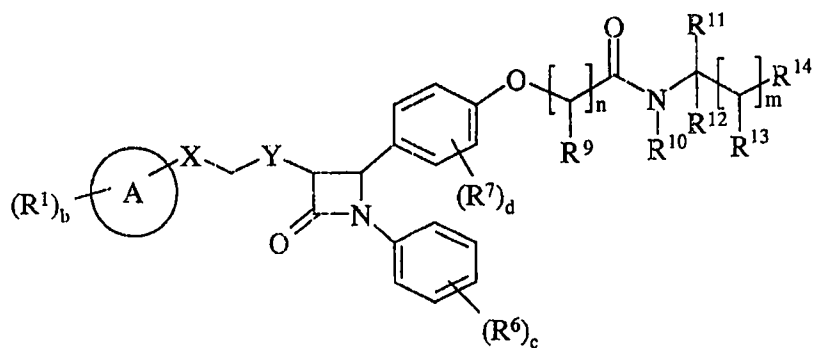


(57) Abstract: Compounds of formula (I); (wherein variable groups are as defined within) pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof and their use as cholesterol absorption inhibitors for the treatment of hyperlipidaemia are described. Processes for their manufacture and pharmaceutical compositions containing them are also described.

WO 2004/005247 A1

Claims

1. A compound of formula (I):



(I)

5

wherein:

Ring A is selected from phenyl or thienyl;

X is selected from $-\text{CR}^2\text{R}^3-$, $-\text{O}-$, $-\text{NR}^x-$ and $-\text{S}(\text{O})_a-$; wherein R^x is hydrogen or C_{1-6} alkyl, and a is 0-2;

- 10 **Y** is selected from $-\text{CR}^4\text{R}^5-$, $-\text{O}-$, $-\text{NR}^2-$ and $-\text{S}(\text{O})_a-$; wherein R^2 is hydrogen or C_{1-6} alkyl, and a is 0-2; wherein there is at least one $-\text{CR}^2\text{R}^3-$ or $-\text{CR}^4\text{R}^5-$ group;

R¹ is independently selected from halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkyl $\text{S}(\text{O})_a$ wherein a is 0 to 2; wherein R^1 is independently optionally substituted on carbon by one or more halo, C_{1-6} alkoxy and hydroxy;

- 15 **b** is 0-3; wherein the values of R^1 may be the same or different;

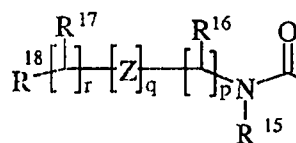
R² and **R³** are independently selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkanoyloxy; wherein R^2 and R^3 may be independently optionally substituted on carbon by one or more halo or hydroxy; or R^2 and R^3 together form an oxo group;

- R⁴** and **R⁵** are independently selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy
20 and C_{1-6} alkanoyloxy; or R^4 and R^5 together form an oxo group;

R⁶ is independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, formyl, carbamoyl, carbamoyloxy, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkenyloxy, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, C_{1-6} alkanoyl- N -(C_{1-6} alkyl)amino,
25 C_{1-6} alkylsulphonylamino, C_{1-6} alkylsulphonyl- N -(C_{1-6} alkyl)amino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, N -(C_{1-6} alkyl)carbamoyloxy, N,N -(C_{1-6} alkyl)₂carbamoyloxy, C_{1-6} alkyl $\text{S}(\text{O})_a$ wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, C_{1-6} alkoxycarbonylamino,

- C₁₋₆alkoxycarbonyl-*N*-(C₁₋₆alkyl)amino, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkoxycarbonylamino, ureido, *N'*-(C₁₋₆alkyl)ureido, *N*-(C₁₋₆alkyl)ureido, *N',N'*-(C₁₋₆alkyl)₂ureido, *N'*-(C₁₋₆alkyl)-*N*-(C₁₋₆alkyl)ureido, *N',N'*-(C₁₋₆alkyl)₂-*N*-(C₁₋₆alkyl)ureido, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl and phenyl; wherein R⁷ is
- 5 independently optionally substituted on carbon by one or more halo, C₁₋₆alkoxy, hydroxy, amino, carboxy, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkanoylamino, C₁₋₆alkanoyl-*N*-(C₁₋₆alkyl)amino, phenyl, phenoxy, benzoyl, phenylC₁₋₆alkyl and phenylC₁₋₆alkoxy;
- c is 0-5; wherein the values of R⁶ may be the same or different;
- 10 R⁷ is independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and
- 15 *N,N*-dimethylsulphamoyl;
- d is 0-4; wherein the values of R⁷ may be the same or different;
- R⁹ is hydrogen, C₁₋₄alkyl, carbocyclyl or heterocyclyl; wherein R⁹ may be optionally substituted on carbon by one or more substituents selected from R²³; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group
- 20 selected from R²⁴;
- R¹⁰ is hydrogen or C₁₋₄alkyl;
- R¹¹ and R¹² are independently selected from hydrogen, C₁₋₄alkyl, carbocyclyl or heterocyclyl; or R¹¹ and R¹² together form C₂₋₆alkylene; wherein R¹¹ and R¹² or R¹¹ and R¹² together may be independently optionally substituted on carbon by one or more substituents
- 25 selected from R²⁵; and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R²⁶;
- R¹³ is hydrogen, C₁₋₄alkyl, carbocyclyl or heterocyclyl; wherein R¹³ may be optionally substituted on carbon by one or more substituents selected from R²⁷; and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or
- 30 more R²⁸;
- R¹⁴ is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, C₁₋₁₀alkoxycarbonyl, C₁₋₁₀alkanoyl, C₁₋₁₀alkanoyloxy, *N*-(C₁₋₁₀alkyl)amino,

- N,N*-(C₁₋₁₀alkyl)₂amino, *N,N,N*-(C₁₋₁₀alkyl)₃ammonio, C₁₋₁₀alkanoylamino, *N*-(C₁₋₁₀alkyl)carbamoyl, *N,N*-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2, *N*-(C₁₋₁₀alkyl)sulphamoyl, *N,N*-(C₁₋₁₀alkyl)₂sulphamoyl, *N*-(C₁₋₁₀alkyl)sulphamoylamino, *N,N*-(C₁₋₁₀alkyl)₂sulphamoylamino, C₁₋₁₀alkoxycarbonylamino, carbocyclyl,
- 5 carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl, carbocyclyl-(C₁₋₁₀alkylene)_e-R²⁹-(C₁₋₁₀alkylene)_f, heterocyclyl-(C₁₋₁₀alkylene)_g-R³⁰-(C₁₋₁₀alkylene)_h, carboxy, sulphy, sulphino, phosphono, -P(O)(OR³¹)(OR³²), -P(O)(OH)(OR³¹), -P(O)(OH)(R³¹) or -P(O)(OR³¹)(R³²) wherein R³¹ and R³² are independently selected from C₁₋₆alkyl; wherein R¹⁴ may be optionally substituted on
- 10 carbon by one or more substituents selected from R³³; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁴; or R¹⁴ is a group of formula (IA):



(IA)

- 15 wherein:

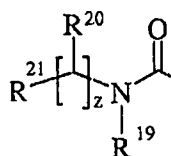
Z is -N(R³⁵)-, -N(R³⁵)C(O)-, -O-, and -S(O)_a-; wherein a is 0-2 and R³⁵ is hydrogen or C₁₋₄alkyl;

R¹⁵ is hydrogen or C₁₋₄alkyl;

- R¹⁶ and R¹⁷ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0 to 2, C₁₋₆alkoxycarbonyl, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl, carbocyclyl, heterocyclyl, sulphy, sulphino, amidino, phosphono,
- 20 -P(O)(OR³⁶)(OR³⁷), -P(O)(OH)(OR³⁶), -P(O)(OH)(R³⁶) or -P(O)(OR³⁶)(R³⁷), wherein R³⁶ and R³⁷ are independently selected from C₁₋₆alkyl; wherein R¹⁶ and R¹⁷ may be independently optionally substituted on carbon by one or more substituents selected from R³⁸; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁹;

- 30 R¹⁸ is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl,

- C₁₋₁₀alkoxy, C₁₋₁₀alkanoyl, C₁₋₁₀alkanoyloxy, *N*-(C₁₋₁₀alkyl)amino, *N,N*-(C₁₋₁₀alkyl)₂amino, C₁₋₁₀alkanoylamino, *N*-(C₁₋₁₀alkyl)carbamoyl, C₁₋₁₀alkoxycarbonyl, *N,N*-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2, *N*-(C₁₋₁₀alkyl)sulphamoyl, *N,N*-(C₁₋₁₀alkyl)₂sulphamoyl, *N*-(C₁₋₁₀alkyl)sulphamoylamino,
- 5 *N,N*-(C₁₋₁₀alkyl)₂sulphamoylamino, carbocyclyl, carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl, carbocyclyl-(C₁₋₁₀alkylene)_e-R⁴⁰-(C₁₋₁₀alkylene)_f or heterocyclyl-(C₁₋₁₀alkylene)_g-R⁴¹-(C₁₋₁₀alkylene)_h, carboxy, sulphy, sulphino, phosphono, -P(O)(OR⁴²)(OR⁴³), -P(O)(OH)(OR⁴²), -P(O)(OH)(R⁴²) or -P(O)(OR⁴²)(R⁴³) wherein R⁴² and R⁴³ are independently selected from C₁₋₆alkyl; wherein R¹⁸ may be optionally substituted on
- 10 carbon by one or more substituents selected from R⁴⁴; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R⁴⁵; or R¹⁸ is a group of formula (IB):



(IB)

- 15 wherein:

R¹⁹ is selected from hydrogen or C₁₋₄alkyl;

- R²⁰ is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino,
- 20 C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0 to 2, C₁₋₆alkoxycarbonyl, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl, carbocyclyl, heterocyclyl, sulphy, sulphino, amidino, phosphono, -P(O)(OR⁴⁶)(OR⁴⁷), -P(O)(OH)(OR⁴⁶), -P(O)(OH)(R⁴⁶) or -P(O)(OR⁴⁶)(R⁴⁷), wherein R⁴⁶ and R⁴⁷ are independently selected from C₁₋₆alkyl; where R²⁰ may be independently optionally
- 25 substituted on carbon by one or more substituents selected from R⁴⁸; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R⁴⁹;

R²¹ is selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy,

- 30 C₁₋₁₀alkoxycarbonyl, C₁₋₁₀alkanoyl, C₁₋₁₀alkanoyloxy, *N*-(C₁₋₁₀alkyl)amino, *N,N*-(C₁₋₁₀alkyl)₂amino, *N,N,N*-(C₁₋₁₀alkyl)₃ammonio, C₁₋₁₀alkanoylamino,

- 117 -

- N*-(C₁₋₁₀alkyl)carbamoyl, *N,N*-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)₂ wherein a is 0 to 2, *N*-(C₁₋₁₀alkyl)sulphamoyl, *N,N*-(C₁₋₁₀alkyl)₂sulphamoyl, *N*-(C₁₋₁₀alkyl)sulphamoylamino, *N,N*-(C₁₋₁₀alkyl)₂sulphamoylamino, C₁₋₁₀alkoxycarbonylamino, carbocyclyl, carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl,
- 5 carbocyclyl-(C₁₋₁₀alkylene)_e-R⁵⁰-(C₁₋₁₀alkylene)_f, heterocyclyl-(C₁₋₁₀alkylene)_g-R⁵¹-(C₁₋₁₀alkylene)_h, carboxy, sulfo, sulphino, phosphono, -P(O)(OR⁵²)(OR⁵³), -P(O)(OH)(OR⁵²), -P(O)(OH)(R⁵²) or -P(O)(OR⁵³)(R⁵³) wherein R⁵² and R⁵³ are independently selected from C₁₋₆alkyl; wherein R²¹ may be independently optionally substituted on carbon by one or more R⁵⁴; and wherein if said heterocyclyl contains an -NH-
- 10 group, that nitrogen may be optionally substituted by a group selected from R⁵⁵;
- p is 1-3; wherein the values of R¹⁶ may be the same or different;
- q is 0-1;
- r is 0-3; wherein the values of R¹⁷ may be the same or different;
- m is 0-2; wherein the values of R¹³ may be the same or different;
- 15 n is 1-2; wherein the values of R⁹ may be the same or different;
- z is 0-3; wherein the values of R²⁰ may be the same or different;
- R²³, R²⁵, R²⁷, R³³, R³⁸, R⁴⁴, R⁴³ and R⁵⁴ are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, C₁₋₁₀alkanoyl, C₁₋₁₀alkanoyloxy,
- 20 C₁₋₁₀alkoxycarbonyl, *N*-(C₁₋₁₀alkyl)amino, *N,N*-(C₁₋₁₀alkyl)₂amino, *N,N,N*-(C₁₋₁₀alkyl)₃ammonio, C₁₋₁₀alkanoylamino, *N*-(C₁₋₁₀alkyl)carbamoyl, *N,N*-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2, *N*-(C₁₋₁₀alkyl)sulphamoyl, *N,N*-(C₁₋₁₀alkyl)₂sulphamoyl, *N*-(C₁₋₁₀alkyl)sulphamoylamino, *N,N*-(C₁₋₁₀alkyl)₂sulphamoylamino, C₁₋₁₀alkoxycarbonylamino, carbocyclyl,
- 25 carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl, carbocyclyl-(C₁₋₁₀alkylene)_e-R⁵⁶-(C₁₋₁₀alkylene)_f, heterocyclyl-(C₁₋₁₀alkylene)_g-R⁵⁷-(C₁₋₁₀alkylene)_h, carboxy, sulfo, sulphino, amidino, phosphono, -P(O)(OR⁵⁸)(OR⁵⁹), -P(O)(OH)(OR⁵⁸), -P(O)(OH)(R⁵⁸) or -P(O)(OR⁵⁹)(R⁵⁹), wherein R⁵⁸ and R⁵⁹ are independently selected from C₁₋₆alkyl; wherein R²³, R²⁵, R²⁷, R³³,
- 30 R³⁸, R⁴⁴, R⁴⁸ and R⁵⁴ may be independently optionally substituted on carbon by one or more R⁶⁰; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R⁶¹;

- 118 -

R^{24} , R^{26} , R^{28} , R^{34} , R^{39} , R^{45} , R^{49} , R^{55} and R^{61} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, sulphonyl, N -(C_{1-6} alkyl)sulphonyl, N,N -(C_{1-6} alkyl)₂sulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, benzyl, phenethyl, benzoyl, phenylsulphonyl and phenyl;

- 5 R^{29} , R^{30} , R^{40} , R^{41} , R^{50} , R^{51} , R^{56} and R^{57} are independently selected from -O-, -NR⁶²-, -S(O)_x-, -NR⁶²C(O)NR⁶³-, -NR⁶²C(S)NR⁶³-, -OC(O)N=C-, -NR⁶²C(O)- or -C(O)NR⁶²-; wherein R^{62} and R^{63} are independently selected from hydrogen or C_{1-6} alkyl, and x is 0-2;

- R^{60} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphonyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, 10 ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, dimethylamino, N -methylcarbamoyl, N,N -dimethylcarbamoyl, methylthio, methylsulphonyl, mesyl, N -methylsulphonyl and N,N -dimethylsulphonyl; and e, f, g and h are independently selected from 0-2;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

15

2. A compound of formula (I) according to claim 1 wherein X is selected from -CH₂-, -CH(OH)-, -C(O)-, -O-, -S-, -S(O)- and -S(O)₂-; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

- 20 3. A compound of formula (I) according to either of claims 1 or 2 wherein Y is -CH₂-, -S- or -S(O)-; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

4. A compound of formula (I) according to any one of claims 1 to 3 wherein R^1 is halo; 25 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

5. A compound of formula (I) according to any one of claims 1 to 4 wherein b is 0-1; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

- 30 6. A compound of formula (I) according to any one of claims 1 to 5 wherein R^6 is halo; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

7. A compound of formula (I) according to any one of claims 1 to 6 wherein c is 0-1; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
8. A compound of formula (I) according to any one of claims 1 to 7 wherein d is 0; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
9. A compound of formula (I) according to any one of claims 1 to 8 wherein R⁹ is hydrogen; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
10. A compound of formula (I) according to any one of claims 1 to 9 wherein R¹⁰ is hydrogen; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
11. A compound of formula (I) according to any one of claims 1 to 10 wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₄alkyl or carbocyclyl; wherein R¹¹ and R¹² may be independently optionally substituted on carbon by one or more substituents selected from R²⁵; wherein R²⁵ is selected from hydroxy, amino, carbamoyl, C₁₋₁₀alkoxycarbonyl, C₁₋₁₀alkoxycarbonylamino, carbocyclyl or carboxy; wherein R²⁵ may be optionally substituted on carbon by one or more R⁶⁰; wherein R⁶⁰ is hydroxy; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
12. A compound of formula (I) according to any one of claims 1 to 11 wherein R¹³ is hydrogen; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
13. A compound of formula (I) according to any one of claims 1 to 12 wherein R¹⁴ is hydroxy, C₁₋₁₀alkyl, C₁₋₁₀alkoxy, C₁₋₁₀alkoxycarbonyl, carboxy or sulphy; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R³³; or R¹⁴ is a group of formula (IIA) (as depicted above) wherein:
- R¹⁵ is hydrogen;
- R¹⁶ and R¹⁷ are independently selected from hydrogen, carboxy, C₁₋₆alkyl and C₁₋₆alkoxycarbonyl;

R^{18} is selected from hydroxy, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} alkoxycarbonyl, carboxy and sulpho;

p is 1;

q is 0;

5 r is 0 or 1;

m is 0 or 1;

n is 1; and

R^{33} is hydroxy;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

10

14. A compound of formula (I) according to any one of claims 1 to 13 wherein m is 0 or 1; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

15. A compound of formula (I) according to any one of claims 1 to 14 wherein n is 1; or a
15 pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

16. A compound of formula (I) (as depicted in claim 1) wherein:

Ring A is selected from phenyl or thienyl;

X is selected from $-CH_2-$, $-CH(OH)-$, $-C(O)-$, $-O-$, $-S-$, $-S(O)-$ and $-S(O)_2-$;

20 Y is $-CH_2-$, $-S-$ or $-S(O)-$;

R^1 is fluoro;

b is 0-1;

R^6 is fluoro;

c is 0-1;

25 d is 0;

R^9 is hydrogen;

R^{10} is hydrogen;

One of R^{11} and R^{12} is hydrogen and the other is selected from hydrogen, methyl, hydroxymethyl, 2-carbamoyl ethyl, 2-(ethoxycarbonyl)ethyl, 2-carboxyethyl,
30 4-(*t*-butoxycarbonylamino)butyl, 4-aminobutyl, isobutyl, phenyl, 4-hydroxyphenyl and 4-hydroxybenzyl;

R^{13} is hydrogen;

R^{14} is hydroxy, pentyl, methoxy, ethoxycarbonyl, *t*-butoxycarbonyl, carboxy or sulpho; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33} ; or R^{14} is a group of formula (IA) (as depicted above) wherein:

R^{15} is hydrogen;

5 R^{16} and R^{17} are independently selected from hydrogen, carboxy, C_{1-6} alkyl and *t*-butoxycarbonyl;

R^{18} is selected from hydroxy, methyl, *t*-butoxy, ethoxycarbonyl, *t*-butoxycarbonyl, carboxy and sulpho;

p is 1;

10 q is 0;

r is 0 or 1;

m is 0 or 1;

n is 1; and

R^{33} is hydroxy;

15 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

17. A compound of formula (I) (as depicted in claim 1) selected from:

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(*R*)- α -{*N*-(*S*)-[1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl]carbamoylmethoxy]phenyl}azetidin-2-one;

20 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(*R*)- α -(carboxy)benzyl]carbamoylmethoxy}phenyl}azetidin-2-one;

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one;

25 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(*N*-(carboxymethyl)carbamoylmethyl]carbamoylmethoxy}phenyl}azetidin-2-one;

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(2-hydroxyethyl)carbamoylmethoxy]phenyl}azetidin-2-one;

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(2-methoxyethyl)carbamoylmethoxy]phenyl}azetidin-2-one;

30 3-(*R*)-4-(*R*)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one;

3-(*R*)-4-(*R*)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one;

3-(R)-4-(R)-1-(phenyl)-3-[2-(thien-3-yl)-2-hydroxyethylsulphanyl]-4-{4-[N-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one;

3-(R)-4-(R)-1-(phenyl)-3-[2-(thien-3-yl)-2-hydroxyethylsulphanyl]-4-{4-[N-((R)- α -{N-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one;

5 3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-{4-[N-((R)- α -{N-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one;

and

3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[N-((R)- α -{N-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-

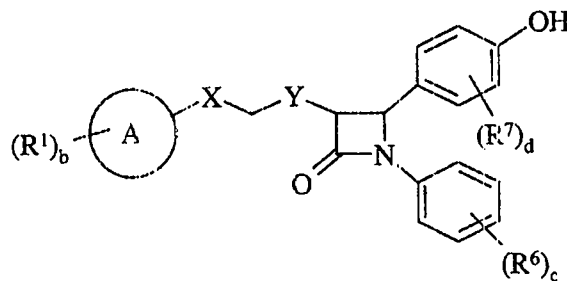
10 one;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

18. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable

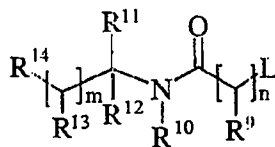
15 groups are, unless otherwise specified, as defined in claim 1) comprises of:

Process 1) reacting a compound of formula (II):



(II)

with a compound of formula (III):

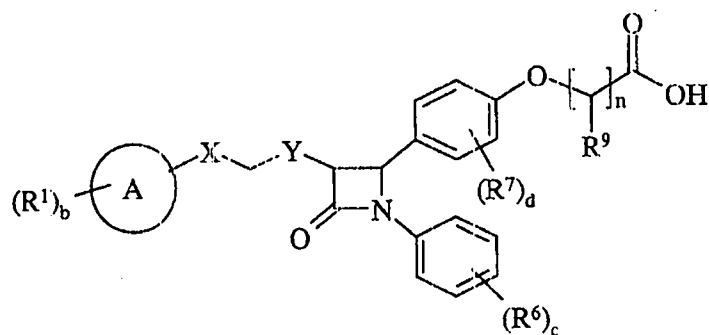


(III)

wherein L is a displaceable group;

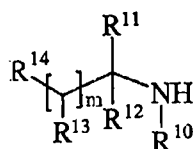
Process 2) reacting an acid of formula (IV):

- 123 -



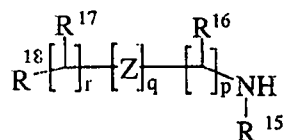
(IV)

or an activated derivative thereof; with an amine of formula (V):



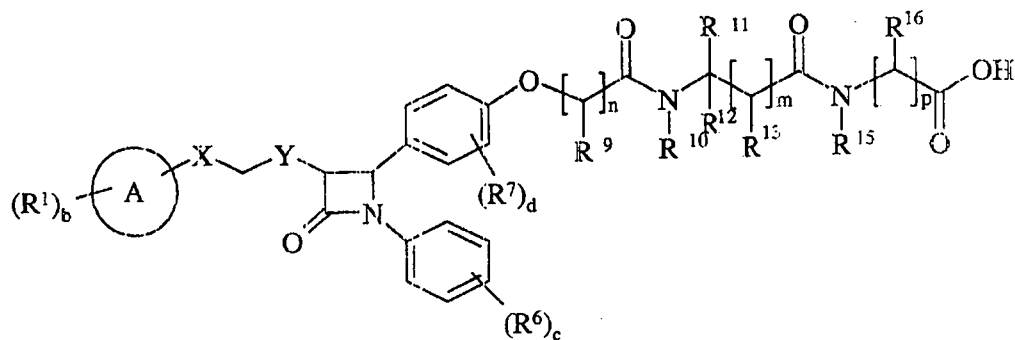
(V)

Process 3): for compounds of formula (I) wherein R^{14} is a group of formula (IIA); reacting a compound of formula (VI) wherein R^{14} is carboxy, or an activated derivative thereof, with an amine of formula (VI):



(VI)

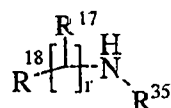
Process 4): for compounds of formula (I) wherein R^{14} is a group of formula (IA), Z is $-N(R^{35})C(O)-$ and q is 1; reacting an acid of formula (VII):



(VII)

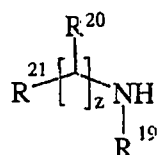
or an activated derivative thereof; with an amine of formula (VIII):

- 124 -



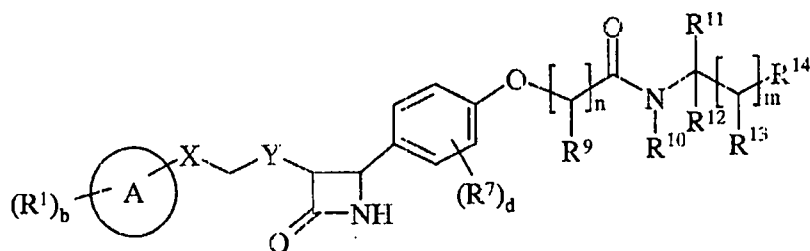
(VIII)

Process 5): for compounds of formula (I) wherein R¹⁴ is a group of formula (IA) and R¹⁸ is a group of formula (IB); reacting an acid of formula (I) wherein R¹⁴ is a group of formula (IA) and R¹⁸ is carboxy, or an activated derivative thereof, with an amine of formula (IX)



(IX)

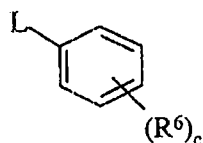
Process 6): reacting a compound of formula (X):



(X)

10

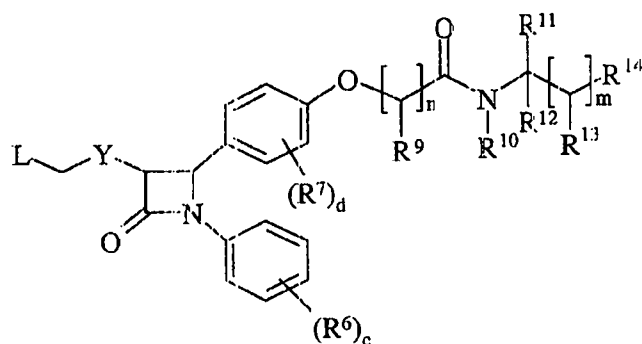
with a compound of formula (XI):



(XI)

wherein L is a displaceable group;

15 Process 7): for compounds of formula (I) wherein X is selected from -O-, -NR^x- and -S(O)_a- wherein a is 0; reacting a compound of formula (XII):



(XII)

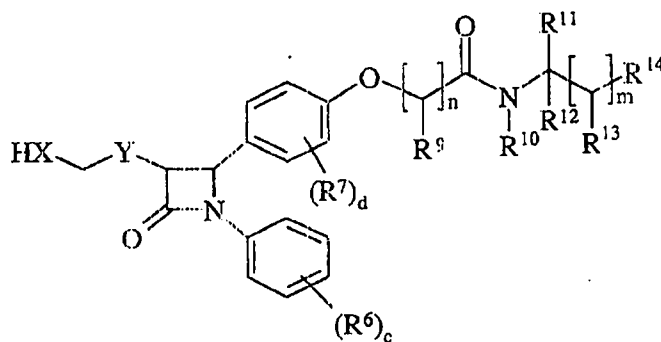
wherein L is a displaceable group; with a compound of formula (XIII):



(XIII)

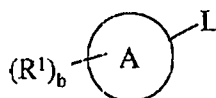
5

Process 8): for compounds of formula (I) wherein X is selected from -O-, -NR^x- and -S(O)_a- wherein a is 0; reacting a compound of formula (XIV):



(XIV)

10 with a compound of formula (XV):

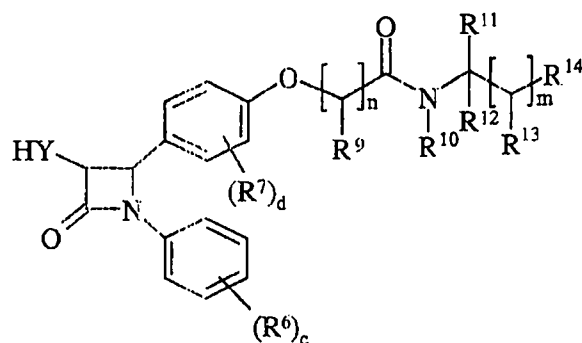


(XV)

wherein L is a displaceable group;

Process 9): for compounds of formula (I) wherein Y is selected from -O-, -NR^z- and -S(O)_a-

15 wherein a is 0; reacting a compound of formula (XVI):



(XVI)

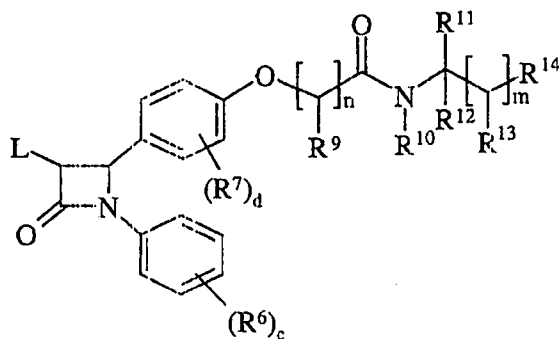
with a compound of formula (XVII):



(XVII)

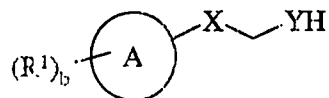
wherein L is a displaceable group;

Process 10): for compounds of formula (I) wherein Y is selected from -O-, -NR²- and -S(O)_a- wherein a is 0; reacting a compound of formula (XVIII):



(XVIII)

wherein L is a displaceable group; with a compound of formula (XIX):



(XIX)

Process 11): for compounds of formula (I) wherein X or Y is -S(O)_a- and a is 1 or 2;

- 15 oxidizing a compound of formula (I) wherein X or Y is -S(O)_a- and a is 0 (for compounds of formula (I) wherein a is 1 or 2) or a is 1 (for compounds of formula (I) wherein a is 2);

and thereafter if necessary or desirable:

- i) converting a compound of the formula (I) into another compound of the formula (I);
- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug; or
- iv) separating two or more enantiomers.

5

19. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16, in association with a pharmaceutically-acceptable diluent or carrier.

10

20. A compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16, for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

15 21. A compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16, for use as a medicament.

22. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16, in the production of a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man.

23. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16, in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

24. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16, in the manufacture of a medicament for use in the production of a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man.

30

25. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

5

26. A method for producing a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16.

10

27. A method of treating hyperlipidaemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16.

15

28. A combination of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

20

29. A combination according to claim 28 wherein the HMG Co-A reductase inhibitors is selected from fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, pitvastatin, mevastatin and rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

25

30. A pharmaceutical composition which comprises a combination according to either of claims 28 or 29, in association with a pharmaceutically acceptable diluent or carrier.

31. The use of a combination according to either of claims 28 or 29, in the production of a
30 cholesterol lowering effect in a warm-blooded animal, such as man.

32. The use of a combination according to either of claims 28 or 29, in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

33. The use of a combination according to either of claims 28 or 29, in the manufacture of a medicament for use in the production of a cholesterol lowering effect.

34. The use of a combination according to either of claims 28 or 29, in the manufacture of
5 a medicament for use in the treatment of hyperlipidaemic conditions.

35. A method for producing a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a combination according to either of claims 28 or 29.

10

36. A method of treating hyperlipidaemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a combination according to either of claims 28 or 29.

15